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## Original experimental

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# Development of a new bed-side-test assessing conditioned pain modulation: a test-retest reliability study

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### Abstract

**Background and aims:** Conditioned pain modulation (CPM) is of considerable interest within pain research. Often CPM testing is conducted in experimental settings using complicated instrumentation, thus challenging the implementation in clinical settings. Being able to assess CPM in a fast and reliable way in clinical settings could lead to a new diagnostic tool allowing improved profiling of pain patients.

**Methods:** A test-retest reliability study and a methodological development study were conducted based on different populations. The reliability study included 22 healthy subjects, mean age 23.6 years (SD: 2.4) and the methodological study included 29 healthy subjects, mean age 21.5 years (SD: 1.6). As painful phasic test stimulus, a 6–10 kg handheld, spring-based pressure algometer was applied perpendicularly to the muscle belly of the tibialis anterior muscle for 10 s and as painful tonic conditioning stimulus, 1–2 standard clamps, inducing a force of 1.3 kg, were applied extra-segmentally at the ipsilateral earlobe for 60–120 s. Four different test protocols were evaluated, of which one protocol was investigated for reliability. Test protocol 1 used a 6 kg pressure

algometer as painful phasic test stimulus and a single clamp applied for 60 s as painful tonic conditioning stimulus. Test protocol 2 used a 10 kg pressure algometer as painful phasic test stimulus, and two clamps applied for 60 s as painful tonic conditioning stimulus. Test protocol 3 used a 10 kg pressure algometer as painful phasic test stimulus and a single clamp applied for 120 s as painful tonic conditioning stimulus. Test protocol 4 used a 6 kg pressure algometer as painful phasic test stimulus and a single clamp applied for 120 s as painful tonic conditioning stimulus.

**Results:** None of the stimuli caused any adverse events, e.g. bruises. In the reliability study (test protocol (1), non-significant CPM effects of 0.3 (SD: 1.6) and 0.2 (SD: 1.0) were observed in session 1 and 2, respectively. The intra-class correlations were 0.67 and 0.72 ( $p < 0.01$ ) and limits of agreement (LoA) ranged from –2.76 to 3.31. Non-significant CPM effects of 0.2 (SD: 1.0), –0.1 (SD: 1.1), and 0.0 (SD: 1.2) were observed for test protocol 2, 3, and 4, respectively).

**Conclusions:** The bedside test developed for investigating CPM was feasible and easy to use in healthy volunteers. No significant CPM effects were measured and a large variation in CPM effect ranging from –0.14 to 0.32 was observed. Intra-class correlation (ICC) values for the pressure algometer were interpreted as “good relative reliability” (test protocol 1), and LoA revealed a somewhat low absolute reliability.

**Implications:** The pressure algometer provided reproducible measurements and was useful for inducing phasic test stimuli. Since no significant CPM effects were detected, no recommendations for the bedside test can yet be made. Further examinations will have to establish if the “one size fits all” application of both test and conditioning stimuli is useful. Future bedside studies involving patient populations are warranted to determine the usefulness of the method.

**Keywords:** pain profiling; descending pain modulation; reliability.

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# 1 Introduction

Conditioned pain modulation (CPM) is a measure of the descending pain control system, and the descending inhibitory modulation has been described as the “pain inhibits pain” phenomenon in humans [1, 2]. Descending pathways from the brainstem intermediate inhibition and facilitation of nociceptive spinal cord neurons, and CPM is an indirect estimate of the balance between the facilitating and inhibitory systems [1, 3, 4]. CPM is believed to be involved as one factor involved in the manifestation of pain sensitization. CPM is found impaired in a range of chronic pain patients suffering from temporomandibular disorder, low back pain, fibromyalgia, osteoarthritis and tension-type headaches [5]. Therefore, CPM is suggested to be one of the important mechanisms involved in central sensitization [3, 6, 7].

CPM is measured experimentally in humans using a painful phasic test stimulus (pain threshold or pain rating), followed by a painful tonic conditioning stimulus and then repeating the same painful phasic test stimulus [8, 9]. The difference in pain intensity between the first and the second phasic stimulus is defined as the CPM effect. Several protocols have been proposed for examining CPM, e.g. electrical and heat stimulations, or pressure and cuff algometry as test stimulus, and cold pressor test or cuff algometry as conditioning stimulus [10, 11]. CPM testing is often conducted in experimental settings using complicated instrumentation, thus challenging its clinical implementation. Furthermore, no golden standard CPM testing method exists [11, 12]. A consensus paper from 2014 gave recommendations for CPM testing but also concluded that so far no specific CPM protocol has proven superior to others [9].

Another major impediment to using CPM assessment routinely in clinical settings is the generally large intra- and inter-individual variations [12, 13]. Further, one study found no significant correlations between various CPM protocols. This underlines the variations, which so far have not been explained [12]. Other studies have reported that the CPM effect is not universal, and though most subjects will experience a decrease in pain ratings (or increase in pain threshold), others will report an increase in pain (or decrease in pain threshold) [11].

The many studies showing impaired CPM in patients with chronic pain have been conducted in experimental settings underlining the need to examine CPM in clinical setups [14–17]. Being able to measure CPM in a fast and reliable way in clinical settings could lead to a new diagnostic tool allowing for a better profiling of the patient’s

pain. Further, a reliable method could also assist in choosing the best possible treatment option for the patient.

To our knowledge, no simple and reliable clinical bedside CPM method exists. Therefore, the aims of this study were (1) to evaluate the test-retest reliability of an easy applicable bedside CPM method and (2) to refine the methodology of the developed bedside CPM method.

# 2 Methods

The study was designed as (1) a test-retest reliability study and (2) a methodological development study aiming to refine the developed bedside CPM method. Two cohorts of healthy subjects were included and none of the subjects participated in both studies. Four different test protocols were evaluated.

## 2.1 Subjects

In the reliability study, 22 healthy subjects (15 men) with a mean age of 23.6 years (SD: 2.4) participated (Table 1). For the methodological study, 29 healthy subjects (nine men) with a mean age of 21.5 years (SD: 1.6) were included. The subjects were recruited through postings on the campus of Aalborg University, Denmark. The inclusion criteria for both studies were age between 18 and 40 years, healthy, pain-free on the test day, and able to speak either Danish or English. Furthermore, the subjects were asked not to consume alcohol or medication on the day of the test. The subjects were given detailed written information and verbal explanation and they signed an informed consent before participating in the study. All included subjects completed the studies with no loss to follow-up. The study was approved by the local Ethics Committee (N-20170088) and was conducted according to the declaration of Helsinki. The reliability study followed the GRRAS recommendations [18].

**Table 1:** Demographics

	Reliability study cohort ( <i>n</i> = 22)	Methodological study cohort ( <i>n</i> = 29)
Age (mean ± SD)	23.6 (±2.4)	21.5 (±1.6)
Sex (females, %)	7 (32%)	20 (69%)
Dominant leg side <sup>a</sup> (right, %)	18 (82%)	26 (90%)

<sup>a</sup>Leg side was determined by asking the question “which leg would you use to kick a football”.

## 2.2 Experimental protocol

The same rater (JBL) conducted all tests in both cohorts.

### 2.2.1 Test-retest reliability: test protocol 1

Test protocol 1 was developed through pilot testing of the CPM method. Two assessment sessions were conducted in which the same test setup was used. The subjects were in a supine position and the dominant leg was used as the testing limb. As the painful phasic test stimulus, a 6 kg handheld, spring-based pressure algometer (SMI, Aalborg University, Fig. 1) was applied perpendicularly to the muscle belly of the tibialis anterior muscle for 10 s (measurement 1). The subjects rated the pain intensity on a 0–10 numerical rating scale (NRS, “0” represented “no pain” and “10” represented “worst pain imaginable”). Then a standard clamp, inducing a force of 1.3 kg, was applied extra-segmentally at the ipsilateral earlobe for 60 s as the painful tonic conditioning stimulus. After the 60 s, the subjects were asked to rate the conditioning pain intensity. Finally, the application of the test stimulus was re-introduced (measurement 2), while the clamp was still applied to the earlobe. Subsequently, the subjects rated the pain intensity of the test stimuli over the tibialis anterior. For the second measurement, the test stimulus was applied slightly proximally or distally to the first measurement to minimize any residual and carry over effects of the repeated stimuli. The same approach was repeated



Fig. 1: Pressure algometer and clamp

24–48 h after the first test session to calculate reliability values.

### 2.2.2 Methodological development: test protocols 2, 3, and 4

Following the reliability study, a methodological study (test protocols 2, 3, and 4) was conducted using different test and conditioning stimuli, allowing for evaluation of any differences in CPM effect between the protocols. Each of the test protocols consisted of one assessment session using one of three different test methods. For all test protocols, the subjects were in a supine position and the dominant leg was used as the testing limb. The subjects rated the pain intensities for both test and conditioning stimuli using a visual analogue scale (VAS). The subjects rated the current pain using a slider to mark the pain between one end representing “no pain” and the other end representing “worst pain imaginable”. For all test stimuli at the tibialis anterior, the measurements were applied slightly proximally or distally to each other to minimize any residual and carry over effects of the repeated stimuli. A 10 min. resting period, during which the subjects relaxed in supine position, was introduced to reduce any potential carry-over effects. The sequence of the test setups was randomized for each subject using a random sequence generator.

Test protocol 2: As the painful phasic test stimulus, a 10 kg handheld, spring-based pressure algometer (SMI, Aalborg University) was applied perpendicularly to the muscle belly of the tibialis anterior muscle for 10 s (measurement 1). The subjects were asked to rate the pain intensity of the test stimulus. Then two standard clamps, each inducing a force of 1.3 kg, were applied extra-segmentally at the ipsilateral earlobe for 60 s as the painful tonic conditioning stimulus. After the 60 s, the subjects were asked to rate the conditioning pain intensity. Afterwards, while the clamp was still applied, the phasic test stimulus was re-applied (measurement 2). Subsequently, the subjects rated the pain intensity of the test stimuli in the tibialis anterior.

Test protocol 3: As the painful phasic test stimulus, a 10 kg handheld, spring-based pressure algometer was applied perpendicularly to the muscle belly of the tibialis anterior muscle for 10 s (measurement 1). The subjects were asked to rate the pain intensity of the test stimulus. Then a standard clamp, inducing a force of 1.3 kg, was applied extra-segmentally at the ipsilateral earlobe for 120 s as the painful tonic conditioning stimulus. After the 120 s, the subjects were asked to rate the conditioning pain intensity. Afterwards, while the clamp was still applied, the phasic test stimulus was re-applied (measurement 2).

Subsequently, the subjects rated the pain intensity of the test stimuli in the tibialis anterior.

Test protocols 4: As the painful phasic test stimulus, a 6 kg handheld, spring-based pressure algometer was applied perpendicularly to the tibialis anterior muscle for 10 s (measurement 1). The subjects were asked to rate the pain intensity of the test stimulus. Then, a standard clamp, inducing a force of 1.3 kg, was applied extra-segmentally at the ipsilateral earlobe for 120 s as the painful tonic conditioning stimulus. After the 120 s, the subjects were asked to rate the conditioning pain intensity. Afterwards, while the clamp was still applied, the phasic test stimulus was re-applied (measurement 2). Subsequently, the subjects rated the pain intensity of the test stimuli in the tibialis anterior.

### 2.2.3 Terminology

Measurement 1: Measurement of the pain intensity of the first test stimulus (phasic stimulus).

Measurement 2: Measurement of the pain intensity of the second test stimulus (phasic stimulus) while the conditioning stimulus is applied (tonic stimulus).

CPM effect: A decrease in pain intensity from measurement 1 to measurement 2. Subjects with a CPM effect are defined as “CPM responders”.

### 2.2.4 Data analysis

Intra-class correlation: Reliability between measurement 1 (session 1) and measurement 1 (session 2) and between measurement 2 (session 1) and measurement 2 (session 2) using test protocol 1.

Paired samples *t*-tests were applied for all continuous outcomes. Data are presented as mean ± standard deviation (SD) unless otherwise stated. Furthermore, the CPM effect is presented in relative values as percentages. Paired samples *t*-test for the CPM effect were applied in order to evaluate the statistical significance.

CPM was calculated as the absolute difference in VAS or NRS between measurement 1 (without conditioning stimulus) and measurement 2 (during conditioning stimulus). Positive values indicate an inhibitory CPM effect.

For the reliability study, the relative and absolute reliabilities across the test sessions were calculated using intra-class correlation coefficients (ICC) (ICC 2.1 for absolute agreement), standard error of measurement (SEM) and Bland-Altman plots with limits of agreement (LoA) [19]. ICC reliability coefficients interpreted as less than 0.4 are considered of “poor reliability”, between 0.4 and 0.59 of “fair reliability”, between 0.6 and 0.75 of “good reliability”, and greater than 0.75 of “excellent reliability” [11, 20].

SEM represents the measurement error, which can be interpreted as an estimate of the variation of the measurements if the test was repeated without any underlying change in the subjects.

SD are the standard deviation of the CPM effect in both sessions and the ICC are the relative reliability. SEM represents the same unit as the pain intensity (NRS) and was calculated by means of the following formula [21]:

$$\text{SEM} = \text{SD} \sqrt{1 - \text{ICC}}$$

A significance level of 0.05 was used and 95% confidence intervals (CI) will be presented. All analyses were performed by means of the statistical software SPSS, Version 25.0 (SPSS Inc., Chicago, IL, USA).

## 3 Results

Table 1 reports participant demographics. No adverse events, e.g. bruises or muscle damage, were identified, and all subjects completed all measurements.

### 3.1 Test-retest reliability: test protocol 1

Table 2 reports NRS scores for measurements 1, 2, and conditioning stimuli. The CPM effects in session 1 and

**Table 2:** Conditioned pain modulation effect in the reliability study.

Reliability study cohort—test protocol 1 ( <i>n</i> = 22)				
	Measurement 1	Measurement 2	CPM effect (95% CI)	Conditioning stimuli
NRS (mean ± SD) (session 1)	3.9 (±1.7)	3.6 (±1.6)	0.3 <sup>ns</sup> (−0.37; 1.01)	4.4 (±1.7)
NRS (mean ± SD) (session 2)	3.6 (±2.2)	3.3 (±2.0)	0.2 <sup>ns</sup> (−0.20; 0.66)	3.9 (±1.7)

NRS = numerical rating scale; ns = non-significant; CPM = conditioned pain modulation; CI = confidence intervals. CPM effect is the decrease in pain intensity from measurement 1 to measurement 2.



session 2 were 0.3 (SD: 1.6) and 0.2 (SD: 1.0), respectively; illustrating no significant CPM effect ( $p$ -values: 0.35 and 0.29). This equals a relative decrease in pain intensity of 8.2% and 6.5%. CPM responder rates showed a CPM effect in nine subjects (40%) in session 1 and in 10 subjects (45%) in session 2.

Table 3 reports the test-retest reliability coefficients. The ICCs for measurement 1 and measurement 2 were 0.67 and 0.72, respectively ( $p$ -values: <0.01). Measured in NRS, the SEM values were 1.9 and 2.1 for measurement 1 and 2, respectively (Table 3).

In the Bland-Altman plots, LoA between sessions were -2.3 to 3.0 and -2.8 to 3.3 for measurement 1 and 2, respectively (Figs. 2 and 3). The LoA for the difference in CPM effect between sessions were -2.0 to 2.8 (Fig. 4).

Table 3: Reliability indicators.

Reliability study cohort-protocol 1 ( $n=22$ )		
	ICC (95% CI)	SEM (NRS)
Measurement 1 (session 1 vs. session 2)	0.67 <sup>a</sup> (0.36; 0.85)	1.9
Measurement 2 (session 1 vs. session 2)	0.72 <sup>a</sup> (0.44; 0.87)	2.1

ICC = intra-class correlation coefficient; SEM = standard error of measurement; NRS = numerical rating scale. <sup>a</sup> $p$ -value < 0.05.

3.2 Methodological development: test protocols 2, 3 and 4

Table 4 reports CPM effect for test protocols 2, 3, and 4 and conditioning stimulus for each test protocol. The CPM effects for test protocols 2, 3, and 4 were 0.2 (SD: 1.0), -0.1 (SD: 1.1), and 0.0 (SD: 1.2), respectively ( $p$ -values: 0.29, 0.49, and 1.00). The CPM effect equals a relative decrease in pain intensity of 4.3% in test protocol 2, an increase in pain intensity of 3.3% in test protocol 3, and no changes in pain intensity in test protocol 4. Overall, 13 subjects (45%) in test protocol 2, 11 subjects (38%) in test protocol 3, and 12 subjects (41%) in test protocol 4 could be categorized as CPM responders.

4 Discussion

The present study found that a newly developed bed-side-test for investigating CPM was feasible, easy and fast to use in healthy volunteers and showed ICC scores interpreted as “good relative reliability” (test protocol 1). When reviewing the absolute reliability, the LoA indicated a somewhat low absolute reliability. A large intra-individual variation in CPM effect (from -0.1 to 0.3) was observed and no significant CPM effect could be observed. CPM responder rates were between 38 and 45% across the test sessions. Despite our efforts to refine the methodology,

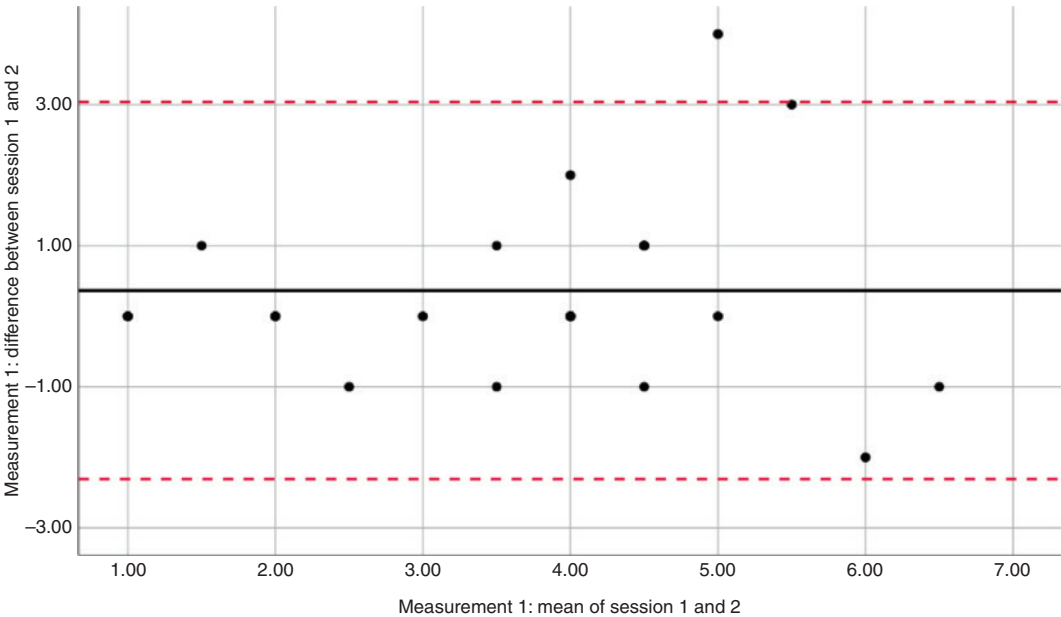
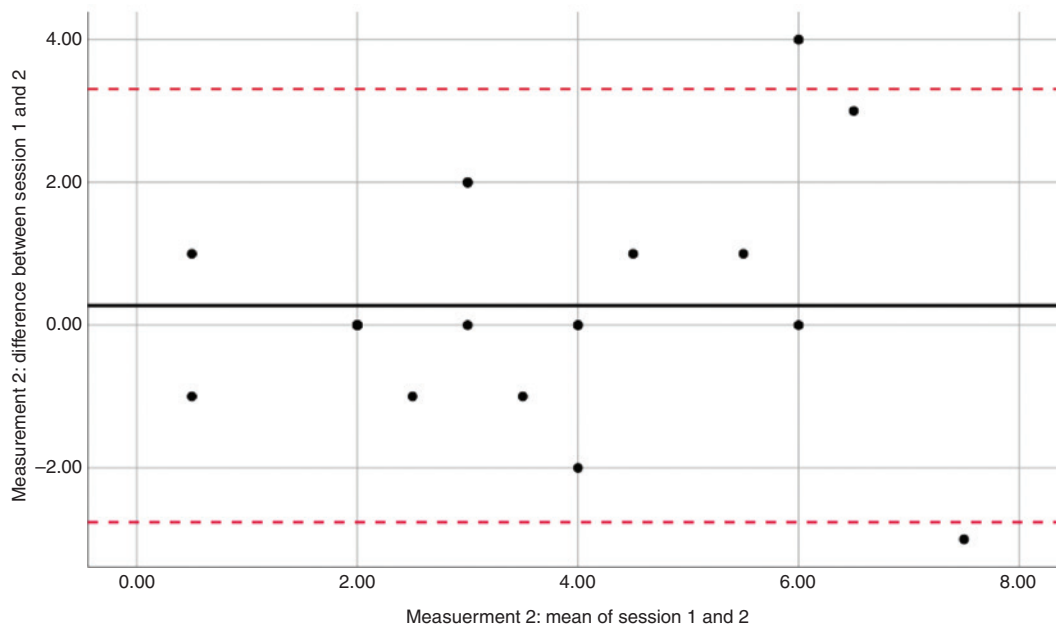
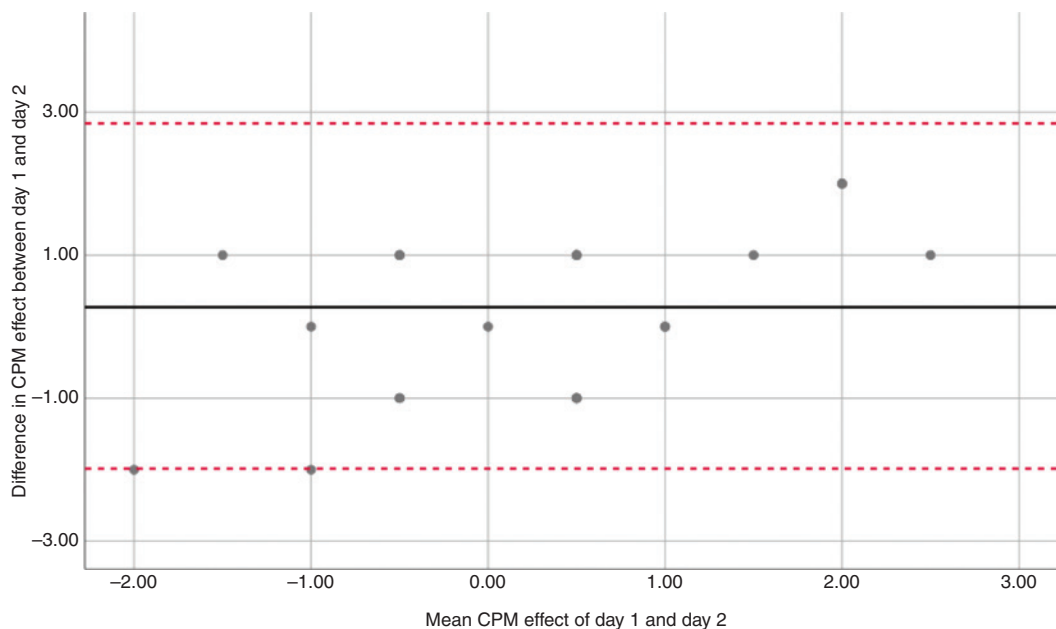


Fig. 2: Bland-Altman plot and limits of agreement for measurement 1 in the reliability study. Values are pain intensities measured with numerical rating scale.



**Fig. 3:** Bland-Altman plot and limits of agreement for measurement 2 in the reliability study. Values are pain intensities measured with numerical rating scale.



**Fig. 4:** Bland-Altman plot and limits of agreement for the between-session CPM effect in the reliability study. Values are pain intensities measured with numerical rating scale.

**Table 4:** Conditioned pain modulation effects in the methodological study.

Methodological study cohort—test protocols 2, 3 and 4 ( $n=29$ )				
	Measurement 1	Measurement 2	CPM effect (95% CI)	Conditioning stimuli
VAS (mean $\pm$ SD) (test protocol 2)	4.5 ( $\pm$ 2.2)	4.3 ( $\pm$ 2.1)	0.2 <sup>ns</sup> (−0.17; 0.55)	2.9 ( $\pm$ 1.8)
VAS (mean $\pm$ SD) (test protocol 3)	4.3 ( $\pm$ 2.1)	4.4 ( $\pm$ 2.0)	−0.1 <sup>ns</sup> (−0.55; 0.28)	2.2 ( $\pm$ 1.7)
VAS (mean $\pm$ SD) (test protocol 4)	2.4 ( $\pm$ 1.6)	2.4 ( $\pm$ 1.6)	0.0 <sup>ns</sup> (−0.45; 0.45)	2.4 ( $\pm$ 1.6)

See method section for description of test protocols. VAS=visual analog scale; SD=standard deviation; ns=non-significant; CI=confidence intervals. Conditioned Pain Modulation effect is defined as the decrease in pain intensity from measurement 1 to measurement 2.

no stronger CPM effect could be retrieved from the modifications made (test protocols 2, 3, and 4). Therefore, no further reliability testing was required.

## 4.1 Reliability study

Our study observed a CPM effect of 6–8% in the different sessions. This is lower than in the study by Graven-Nielsen et al., which observed a CPM effect of 13–18% for pressure pain tolerance and pressure pain threshold when using cuff-induced pain as conditioning stimulus and cuff pressure algometry as test stimulus [22]. Nahman-Averbuch et al. observed a CPM effect varying from 0 to 56% with heat as conditioning stimulus and various test stimuli (heat pain, pressure pain threshold, temporal summation) [12]. Discrepancies could be explained by the different use of test and conditioning stimuli in different intensity ranges. In the present study, pressure pain was used as both test and conditioning stimulus. The paradigm was applied as a “one size fits all” method with same magnitude of force being applied to all subjects as this is the approach most likely to be used for a simple bedside test. Recently, a study by Schliessbach et al. concluded that a decrease in pain threshold after a conditioning stimulus was seen in more than 10% of healthy subjects and that this does not necessarily indicate an abnormal finding [23]. In line with the present study, several other studies have reported large intra-individual variation in CPM effects in healthy subjects [12, 13, 23, 24], indicating that CPM might not be a particularly stable measurement.

Various CPM protocols have revealed different ICC values and have reported different statistics, such as SEM or LoA [11, 13]. A systematic review examining reliability of different CPM protocols ranged the relative reliability of the test stimulus from good-to-excellent when using pressure pain threshold as stimulus [11]. The review also reported that when using subjective pain rating for heat pain as test stimulus, the relative reliability was lower and ranged from poor-to-fair. In the present study, the ICC values were interpreted as “good relative reliability” (ICC 0.67–0.72) according to the recommendations [11, 20]. The measurements revealed similar ICC values for the test stimulus; both with and without conditioning stimulus. These values are similar to other studies examining the relative reliability of a test stimulus with and without conditioning stimulus [11, 13]. This implies that the bedside algometer test is reproducible. The absolute reliability can be measured as SEM, which provides a value for the measurement error in the same unit as the

measurement itself [21]. This study observed SEM values for measurements 1 and 2 of 1.9 and 2.1, respectively. To our knowledge, no other studies have investigated SEM of subjective pain ratings during CPM testing. The Bland-Altman plots show similar LoA between measurements and for the CPM effect. The high values indicate large intra-individual variation, which again indicates that the absolute reliability was somewhat low. Thus, it was not possible to evoke a reliable CPM effect in this population of healthy subjects. The LoA observed in the study were lower than in Lie et al. [24]. These authors reported LoAs ranging from –3.4 to 3.3 and from –4.3 to 3.2 for the test stimulus and from –2.3 to 3.2 for the CPM effect, indicating a somewhat lower absolute reliability than in the present study.

## 4.2 Test stimulus

A pressure algometer with the force of either 6 kg or 10 kg was applied as a phasic test stimulus to induce pain. As expected, the 10 kg force resulted in higher pain ratings. However, the pain ratings only increased from 3.6 to 3.9 with the 6 kg force and from 4.3 to 4.5 with the 10 kg force, which is regarded a somewhat small increase. This could indicate that once a test stimulus exceeds the pain threshold, a quite substantial increase in the test stimulus is needed to further increase the pain rating in healthy subjects when using a localized pressure stimulus. Future studies are needed to examine whether this phenomenon is apparent in patients with chronic pain or whether more severe pain increases can be observed with higher test stimuli. The applied test stimuli were fixed to 6 or 10 kg and not individually based. Thus, large variations of pain ratings were seen. It is unknown whether this “one size fits all” approach could influence the CPM effect. However, when examining the individual data from the participants, no tendency towards higher test stimulus pain ratings leading to larger CPM effect or vice versa were observed.

As the outcome measure for subjective pain rating, both VAS and NRS were used. These methods have been shown to measure almost the exact same pain intensities when used simultaneously [25]. NRS was implemented since it is often used in clinical settings and as it is an easy method to administer for the subjects tested [26]. VAS has commonly been used in other CPM studies [1, 13, 27]. NRS was used in the reliability study. However, since the test stimulus pain ratings were repeated with short intervals, it was considered that the recalling of the first pain rating might bias the second pain rating. Therefore,



a VAS was used in the methodological study since it was considered less prone to bias.

### 4.3 Conditioning stimulus

Previously, a conditioning pain intensity of VAS=4 has been used when evaluating CPM [16]. In the present study, the mean conditioning pain intensity varied from NRS 3.8 to 4.6. A study by Graven-Nielsen et al. [22] showed that different CPM responses could be obtained with the use of different conditioning pain intensities. Therefore, the methodological study introduced the use of two clamps and longer duration of the applied stimuli to increase the evoked conditioning pain intensity. These changes led to a lower conditioning stimulus intensity in the range of VAS 2.2 to 2.9. This was contrary to our expectation as it has previously been observed that stimulation of large areas results in decreased pain threshold, indicating spatial summation [15]. A study by Staud et al. [28] found that when separating the probes used for mechanical pressure by 8 cm, both fibromyalgia patients and healthy subjects reported higher pain intensity compared with separating the probes by 4 cm only. This could indicate that higher pain ratings are more likely to occur when stimulating across spinal segments. However, this is contrary to our test protocol using two clamps applied to the same earlobe. Furthermore, it is possible that some pain adaption occurred during the longer duration of the conditioning stimulus (i.e. more than 60 sec) resulting in lower pain intensities after a prolonged period of conditioning stimulus. In future studies, it is required to evaluate whether a higher conditioning stimulus will induce a larger CPM effect. This could not be examined in the present study despite the attempt to induce higher conditioning pain.

### 4.4 CPM responder

Our study defined a subject as a CPM responder when experiencing a CPM effect during the test, which ranged from 38 to 45% of the subjects. A study by Schliessbach et al. [23] attempted to establish reference values for the CPM effect by evaluating CPM effects at the 5th, 10th and 25th percentiles. The authors found a CPM effect of less than zero at both the 5th and 10th percentiles and concluded that the choice of cut-off value should depend on the particular clinical or scientific question. Fundamentally, such reference values should be statistically determined as z-scores from large normative cohort

studies. The largest CPM study to date based on around 2,000 subjects could be used to define statistical ranges around the mean [29]. The complicated aspect is that the normative data and the size of the CPM responses vary from methodology to methodology. It has also been shown that within the same subjects, different CPM methods elicit different responses and that subjects may be a responder to one method but a non-responder to another method [13, 30]. However, it is evident that the CPM effect is a variable parameter and currently all the many parameters influencing the response are not known.

### 4.5 Limitations

Sex has been shown to have an influence on CPM as several studies have found stronger pain inhibitory capacity in males versus females [31–33]. The two populations in the present study consisted of 68% males in the reliability study and 31% in the methodological study. The reliability study revealed a better CPM effect than the methodological study and this might partly be explained by the inclusion of more males than females. The use of both VAS and NRS to assess pain intensities may have introduced a potential bias in the comparison between groups. Since the purpose was to compare the within-group pain intensity, the possible bias is unlikely to affect the CPM effect.

## 5 Conclusion

A bedside CPM method was developed based on a pressure algometer as phasic test stimulus and a clamp attached to the earlobe as a tonic conditioning stimulus. No significant CPM effects were observed and varying test and conditioning stimuli systematically did not significantly change the CPM effect. The reliability study observed ICC values interpreted as, “good relative reliability” from the bedside pressure algometer. LoA revealed a somewhat low absolute reliability. Future attempts to refine the bedside method should be performed to examine whether a significant CPM effect can be observed in healthy subjects. Furthermore, bedside studies involving patient populations are warranted.

### Authors' statements

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**Conflict of interest:** Authors state no conflict of interest.

**Informed consent:** Informed consent was obtained from all individuals included in this study.

**Ethical approval:** The research related to human use complies with all the relevant national regulations, institutional policies and was conducted in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

## References

- [1] Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Pain* 2015;156:55–61.
- [2] Alsouhibani A, Vaegter HB, Hoeger Bement M. Systemic exercise-induced hypoalgesia following isometric exercise reduces conditioned pain modulation. *Pain Med* 2019;20:180–90.
- [3] Arendt-Nielsen L, Graven-Nielsen T. Translational musculoskeletal pain research. *Best Pract Res Clin Rheumatol* 2011;25:209–26.
- [4] Eitner A, Hofmann GO, Schaible HG. Mechanisms of Osteoarthritic Pain. *Studies in Humans and Experimental Models*. *Front Mol Neurosci* 2017;10:349.
- [5] Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. *J Pain* 2012;13:936–44.
- [6] Arendt-Nielsen L. Joint pain: more to it than just structural damage? *Pain* 2017;158(Suppl 1):S66–73.
- [7] Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2015;23:1043–56.
- [8] Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain* 2010;14:339.
- [9] Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, Landau R, Marchand S, Matre D, Nilsen KB, Stubhaug A, Treede RD, Wilder-Smith OH. Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain* 2015;19:805–6.
- [10] Imai Y, Petersen KK, Morch CD, Arendt Nielsen L. Comparing test-retest reliability and magnitude of conditioned pain modulation using different combinations of test and conditioning stimuli. *Somatosens Mot Res* 2016;33:169–77.
- [11] Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice AS. Reliability of conditioned pain modulation: a systematic review. *Pain* 2016;157:2410–9.
- [12] Nahman-Averbuch H, Yarnitsky D, Granovsky Y, Gerber E, Dagul P, Granot M. The role of stimulation parameters on the conditioned pain modulation response. *Scand J Pain* 2013;4:10–4.
- [13] Vaegter HB, Petersen KK, Morch CD, Imai Y, Arendt-Nielsen L. Assessment of CPM reliability: quantification of the within-subject reliability of 10 different protocols. *Scand J Pain* 2018;18:729–37.
- [14] Skou ST, Graven-Nielsen T, Rasmussen S, Simonsen OH, Laursen MB, Arendt-Nielsen L. Widespread sensitization in patients with chronic pain after revision total knee arthroplasty. *Pain* 2013;154:1588–94.
- [15] Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. *Arthritis Rheum* 2012;64:2907–16.
- [16] Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T. Sensitization in patients with painful knee osteoarthritis. *Pain* 2010;149:573–81.
- [17] Lewis GN, Rice DA, McNair PJ, Kluger M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. *Br J Anaesth* 2015;114:551–61.
- [18] Kottner J, Audige L, Brorson S, Donner A, Gajewski BJ, Hrobjartsson A, Roberts C, Shoukri M, Streiner DL. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. *Int J Nurs Stud* 2011;48:661–71.
- [19] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–10.
- [20] Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86:420–8.
- [21] Donoghue D, Physiotherapy Research and Older People (PROP) group, Stokes EK. How much change is true change? The minimum detectable change of the Berg Balance Scale in elderly people. *J Rehabil Med* 2009;41:343–6.
- [22] Graven-Nielsen T, Izumi M, Petersen KK, Arendt-Nielsen L. User-independent assessment of conditioning pain modulation by cuff pressure algometry. *Eur J Pain* 2017;21:552–61.
- [23] Schliessbach J, Lütolf C, Streitberger K, Scaramozzino P, Arendt-Nielsen L, Curatolo M. Reference values of conditioned pain modulation. *Scand J Pain* 2019;19:279–86.
- [24] Lie MU, Matre D, Hansson P, Stubhaug A, Zwart JA, Nilsen KB. A tonic heat test stimulus yields a larger and more reliable conditioned pain modulation effect compared to a phasic heat test stimulus. *Pain Rep* 2017;2:e626.
- [25] Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, Kvarstein G, Stubhaug A. Assessment of pain. *Br J Anaesth* 2008;101:17–24.
- [26] Fillingim RB, Loeser JD, Baron R, Edwards RR. Assessment of chronic pain: domains, methods, and mechanisms. *J Pain* 2016;17(9 Suppl):T10–20.
- [27] Petersen KK, Graven-Nielsen T, Simonsen O, Laursen MB, Arendt-Nielsen L. Preoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief after total knee replacement. *Pain* 2016;157:1400–6.
- [28] Staud R, Koo E, Robinson ME, Price DD. Spatial summation of mechanically evoked muscle pain and painful aftersensations in normal subjects and fibromyalgia patients. *Pain* 2007;130:177–87.
- [29] Skovbjerg S, Jorgensen T, Arendt-Nielsen L, Ebstrup JF, Carstensen T, Graven-Nielsen T. Conditioned pain modulation and pressure pain sensitivity in the adult danish general population: the DanFunD study. *J Pain* 2017;18:274–84.
- [30] Oono Y, Nie H, Matos RL, Wang K, Arendt-Nielsen L. The inter- and intra-individual variance in descending pain modulation

- evoked by different conditioning stimuli in healthy men. *Scand J Pain* 2011;2:162–9.
- [31] Bossmann T, Brauner T, Wearing S, Horstmann T. Predictors of chronic pain following total knee replacement in females and males: an exploratory study. *Pain Manag* 2017;7:391–403.
- [32] Hermans L, Van Oosterwijck J, Goubert D, Goudman L, Crombez G, Calders P, Meeus M. Inventory of personal factors influencing conditioned pain modulation in healthy people: a systematic literature review. *Pain Pract* 2016;16: 758–69.
- [33] Bulls HW, Freeman EL, Anderson AJ, Robbins MT, Ness TJ, Goodin BR. Sex differences in experimental measures of pain sensitivity and endogenous pain inhibition. *J Pain Res* 2015;8:311–320.